REMARKS

Claims 1-15, 17-22, 24, 34, 43, 56, and 76 were pending. Claims 3, 4, 22, and 76 were previously withdrawn from consideration. Claims 1, 7, 24, 34, 43, and 56 are amended; claims 2 and 6 are canceled without prejudice or disclaimer; and no new claims are added by this Amendment. No new matter is introduced.

Prior Office Action

Applicants acknowledge withdrawal by the Examiner of previous claim rejections under 35 U.S.C. §§ 102(a) and (b) and under 35 U.S.C. § 103. Applicants further acknowledge indication by the Examiner that previous claim rejections under 35 U.S.C. § 112, second paragraph, have also been withdrawn.

Information Disclosure Statements and Forms 1449

In response to Applicants' telephone inquiry into the status of two previously submitted Information Disclosure Statements, received by the U.S. Patent and Trademark Office on October 1, 2001, and September 30, 2002, the Examiner has indicated that these have been lost by the Patent Office. At the request of the Examiner, enclosed herewith are copies of the previously submitted Forms 1449. Because many of the references cited in the two Forms 1449 were non-patent literature documents, copies of the cited references are resubmitted herewith for the sake of expediting prosecution.

In addition to the foregoing, Applicants are submitting a new Information Disclosure Statement as part of the Request for Continued Examination.

Claim Rejections Under 35 U.S.C. § 112, first paragraph (enablement)

The Examiner indicated (page 3) that the specification is enabling for a method for inhibiting B-cell lymphoma tumor growth comprising administering to a subject having a B-cell lymphoma tumor (a) an immunostimulatory nucleic acid sequence that is 6 or more nucleotides in length and comprises an unmethylated CpG motif and further comprises a phosphorothioate modified backbone, wherein said immunostimulatory CpG nucleic acid is administered in an

amount effective to upregulate CD20 expression in said B-cell lymphoma; and (b) an anti-CD20 antibody. However, claims 1, 2, 5-15, and 17-21 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly being not enabling for claims drawn to preventing cancer in a subject; immunostimulatory nucleic acids that are less than 6 nucleotides in length; nucleotides which do not contain an unmethylated CpG motif; and nucleotides which do not contain a modified backbone. The Examiner indicated that, on the basis of his understanding of the art relevant to immunostimulatory nucleic acids, in order for an oligonucleotide to stimulate an immune response in vivo it must contain an unmethylated CpG motif, be at least 6 nucleotides in length, and be protected from nuclease degradation by comprising, for example, modified backbone linkage, such as a phosphorothioate linkage (emphasis added; page 7 of Office Action).

Without meaning to concede the Examiner's position, and solely to advance prosecution, Applicants, in response with respect to claims drawn to preventing cancer in a subject, have amended claim 1 (and claim 24, see below) to remove the "preventing" language. Applicants submit that this amendment is sufficient to overcome the rejection of claim 1 (and claim 24, see below) under 35 U.S.C. § 112, first paragraph (enablement) with respect to preventing cancer in a subject.

Also without meaning to concede the Examiner's position, and solely to advance prosecution, Applicants have amended claim 1 to substitute the term "B-cell malignancy" for the term "cancer". Applicants submit that this amendment is sufficient to overcome the rejection of claim 1 under 35 U.S.C. § 112, first paragraph (enablement) with respect to use of the term "cancer".

With respect to the Examiner's assertion that in order for an oligonucleotide to stimulate an immune response in vivo it must contain an unmethylated CpG motif, be at least 6 nucleotides in length, and be protected from nuclease degradation by comprising, for example, modified backbone linkage, such as a phosphorothioate linkage, Applicants traverse the Examiner's position as to what are required features but nonetheless wish to point out the following. Consistent with the previous election of species and the specification, claim 1 is amended to specify the immunostimulatory nucleic acid is an immunostimulatory CpG oligonucleotide between 6 and 100 nucleotides long comprising at least the formula 5′ $X_1X_2CGX_3X_4$ 3′ wherein C is unmethylated and wherein X_1, X_2, X_3, and X_4 are nucleotides (page 7, lines 18-20; page 40,

lines 14-16). The immunostimulatory nucleic acid thus contains an unmethylated CpG motif and is at least 6 nucleotides in length. Claim 2, specifying the immunostimulatory nucleic acid is a CpG nucleic acid having an unmethylated CpG motif, and claim 6, specifying the immunostimulatory nucleic acid is eukaryotic DNA, are canceled without prejudice or disclaimer.

For the record, as noted by the Examiner on page 8 of the Office Action, the CpG nucleic acid may be represented by at least the formula 5′ $N_1X_1CGX_2N_2$ 3′ wherein X_1 and X_2 are nucleotides and N_1 and N_2 are nucleic sequences made up of from about 0-25 N's each (emphasis added). Thus the CpG nucleic acid, when N_1 and N_2 are made up of 0 N's each, can be as short as 4 nucleotides in length.

Applicants further specifically traverse the Examiner's requirement that the immunostimulatory nucleic acid must be protected from nuclease degradation by comprising, for example, modified backbone linkage, such as a phosphorothioate linkage. At a minimum, the claims should not be limited to phosphorothioate oligonucleotides, as suggested by the Examiner at page 9 of the Office Action, because the specification at pages 41-43 discloses a number of approaches and structures, including but not limited to phosphorothioate modification, that can be used to produce stabilized oligonucleotides. Further, the teaching of Hartmann et al., relied upon by the Examiner for the proposition that the immunostimulatory nucleic acid must be protected from nuclease degradation by comprising, for example, modified backbone linkage, such as a phosphorothioate linkage, discloses only the use of "bare" nucleotides in aqueous solution and does not take into account effects of formulation or dose. For example, page 68, line 22 – page 69, line 3 of the specification discloses, *inter alia*, nucleic acids formulated as nucleic acid delivery complexes, including, for example, nucleic acids encapsulated by liposomes. Furthermore, pharmacokinetic considerations can be overcome by use of increased doses.

Applicants submit that the specification taken as a whole, as well as present amendments to the claims specifying that the immunostimulatory nucleic acids of the invention are immunostimulatory CpG nucleic acids comprising at least the formula 5′ $X_1X_2CGX_3X_4$ 3′, wherein C is unmethylated and wherein X_1, X_2, X_3, and X_4 are nucleotides, adequately address the arguments appearing at pages 5-6 of the Office Action pertaining to gene therapy. Persons of

skill in the art would understand that the claims and the specification are directed to methods of using immunostimulatory CpG nucleic acids which feature the presence of the CpG motif 5′ $X_1X_2CGX_3X_4$ 3′, rather than nucleic acids encoding CD20 or encoding a factor which induces expression of CD20. Therefore, Applicants respectfully traverse the Examiner's reasoning with respect to making an enablement rejection based on the unpredictability of gene therapy.

Applicants also wish to affirm the Examiner's assessment (page 9) that the level of skill in the art is high, further mitigating the argument that the claims are not adequately enabled.

In view of the foregoing, Applicants respectfully request that the enablement rejection of claims 1, 2, 5-15, and 17-21 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Further Claim Rejections Under 35 U.S.C. § 112, first paragraph

The Examiner maintained his rejections of claims 24, 34, 43, and 56 under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description. The Examiner also maintained his rejections of claims 24, 34, 43, and 56 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement.

With respect to the rejections based on alleged lack of adequate written description, it is noted that the Examiner found adequate written description for a large number of immunostimulatory nucleic acids which induce expression of CD20. It is further noted that the Examiner indicated that the specification identifies CD19, CD20, and CD22 as "the only cancer antigens" present in cancerous B-cell lymphomas but to a lesser extent than in normal B cells. The rejections of claims 24, 34, 43, and 56, based on alleged lack of adequate written description, rest on the Examiner's view that the specification does not specifically identify (a) which immunostimulatory nucleic acids are capable of inducing CD19 or CD22 expression on the surface of cancer cells; and (b) which other surface antigens, which are not present or present to a lower extent in B-cell lymphomas than in normal B cells, are to be identified and upregulated by the administration of immunostimulatory nucleic acids.

With respect to the rejections of claims 24, 34, 43, and 56 based on alleged lack of enablement, the Examiner has taken the view that an undue amount of experimentation is required to practice the full scope of the claimed invention because the specification (in the

Examiner's view) (a) does not identify a representative number of immunostimulatory nucleic acids which induce CD19 or CD22 expression in cancer cells; (b) is directed to methods of preventing cancer; and (c) does not identify a representative number of structurally defined cell surface antigens. Furthermore, the Examiner indicated that if the immunostimulatory nucleic acids which induce CD19 or CD22 expression are unmethylated CpG oligonucleotides similar to claims 1, 2, 5-15 and 17-21, then the claims must be limited to immunostimulatory nucleic acids at least 6 nucleotides in length comprising at least one unmethylated CpG motif and comprising a modified backbone to protect the nucleotide from degradation.

Rejections of Claim 24 Under 35 U.S.C. § 112, first paragraph

a) Written Description:

Claim 24 stands rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description. The Examiner alleges on pages 12 and 13 of the Office Action that the specification has not specifically identified which immunostimulatory nucleic acids are capable of inducing CD19 or CD22 expression in cancer cells. Applicants respectfully traverse this rejection for the reasons below.

As noted above, the Examiner found adequate written description for a large number of immunostimulatory nucleic acids which induce expression of CD20. It is to be noted that the detailed description of the invention, at page 11, lines 1-15, specifically discloses, "Now it has been discovered according to the invention that immunostimulatory nucleic acids actually cause the induction of specific antigens CD20, CD19, and CD22, each of which can be targeted by specific antibody therapies." Applicants submit that the large number of immunostimulatory nucleic acids which induce expression of CD20 are further representative of immunostimulatory nucleic acids which induce expression of CD19 and CD22. Therefore Applicants respectfully submit that, contrary to the assertion by the Examiner, the specification has sufficiently described a representative number of species of immunostimulatory nucleic acids which induce the expression of CD19 and/or CD22 on the surface of cancer cells.

Therefore, Applicants respectfully request reconsideration and withdrawal of the written description rejection of claim 24 under 35 U.S.C. § 112, first paragraph.

b) Enablement:

Claim 24 also stands rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner alleges on page 13 of the Office Action that claim 24 encompasses administration of any nucleic acid which induces the expression of CD19 or CD22 in any type of cancer cell, and that in order to make and use the claimed invention, a representative number of immunostimulatory nucleic acids which induce CD19 or CD22 expression in cancer cells would have to be identified. The Examiner goes on to assert that claim 24 is not enabled to the extent that it encompasses preventing cancer. Further, the Examiner makes the assertion, beginning at the bottom of page 14, that if the immunostimulatory nucleic acids which induce CD19 and CD22 expression are the unmethylated CpG oligonucleotides similar to claims 1, 2, 5-15 and 17-21, that the claim must be limited to immunostimulatory nucleic acids at least 6 nucleotides in length comprising at least one unmethylated CpG motif and comprising a modified backbone to protect the nucleotide from degradation. [Emphasis added.] Applicants respectfully traverse this rejection for reasons provided below.

Amendments to claim 24 are believed to overcome the rejection as it pertains to use of the terms "preventing" and "cancer". As discussed above, amended claim 24 no longer recites "preventing". In addition, the claim term "cancer" has been amended to read "B-cell malignancy". Applicants submit that these amendments address the rejection as it pertains to "preventing" and "any cancer".

Claim 24 is also currently amended, in a manner similar to that of claim 1, to specify the immunostimulatory nucleic acid is an immunostimulatory CpG oligonucleotide between 6 and 100 nucleotides long comprising at least the formula 5′ $X_1X_2CGX_3X_4$ 3′, wherein C is unmethylated and wherein X_1, X_2, X_3, and X_4 are nucleotides. As discussed above with respect to claim 1, Applicants submit that the immunostimulatory nucleic acid can but need not necessarily comprise a modified backbone to protect the nucleotide from degradation. Furthermore, as pointed out above in response to the written description rejection of claim 24, Applicants submit that the large number of immunostimulatory nucleic acids which induce expression of CD20 are further representative of immunostimulatory nucleic acids which induce expression of CD19 and CD22. Thus, Applicants submit that the immunostimulatory nucleic acids which induce CD19 and CD22 expression indeed are the unmethylated CpG

oligonucleotides similar to claims 1, 2, 5-15 and 17-21, while the claim need not be limited, as suggested by the Examiner, to immunostimulatory nucleic acids at least 6 nucleotides in length comprising at least one unmethylated CpG motif and comprising a modified backbone to protect the nucleotide from degradation.

In view of the high level of skill in the art, acknowledged by the Examiner, Applicants submit that their disclosure of immunostimulatory nucleic acids that "actually cause the induction of specific antigens CD20, CD19, and CD22, each of which can be targeted by specific antibody therapies" is sufficient to enable claim 24. The disclosure is further enabling, because it also provides detailed guidance on how to implement the claimed invention as discussed above.

Therefore, Applicants respectfully request that the rejection of claim 24 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Rejections of Claim 34 Under 35 U.S.C. § 112, first paragraph

a) Written Description:

Claim 34 stands rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description. The Examiner alleges on page 16 that the claim encompasses B-cell lymphoma specific antigens which have not been adequately described, as well as nucleic acids which have not been identified which induce the expression of the antigens. Applicants respectfully traverse this rejection.

For the record, Applicants wish to point out that the specification discloses that individual immunostimulatory nucleic acids induce or upregulate the expression of a number of cell surface antigens, including, without limitation, CD19, CD20, CD22, CD40, CD54, CD69, CD80, CD86, MHC Class I, MHC Class II (e.g., HLA-DR), surface immunoglobulin (sIg), and 1D10. Applicants submit that these widely recognized and structurally characterized antigens satisfy the written description requirement for the claimed genus. Furthermore, Applicants wish to point out to the Examiner that the immunostimulatory nucleic acids appear to induce expression of such antigens in a manner that does not involve or require selection of a particular oligonucleotide sequence to induce a particular antigen. Applicants submit that the specification clearly discloses these aspects of the invention, and provides common features for useful

antigens and immunostimulatory nucleic acids, as discussed above. Accordingly, Applicants submit that one of skill in the art would recognize that Applicants possessed this invention at the time the application was filed.

The foregoing notwithstanding, and solely for the sake of advancing prosecution, Applicants have amended claim 34 to specify that the surface antigen is selected from CD19, CD20, and CD22. Furthermore, claim 34 is currently amended to specify that the immunostimulatory nucleic acid is an immunostimulatory CpG oligonucleotide between 6 and 100 nucleotides long comprising at least the formula 5′ $X_1X_2CGX_3X_4$ 3′, wherein C is unmethylated and wherein X_1, X_2, X_3, and X_4 are nucleotides. As mentioned previously, the immunostimulatory nucleic acids that induce CD20 are further representative of immunostimulatory nucleic acids which induce expression of CD19 and CD22. Applicants submit that claim 34 as currently amended satisfies the written description requirement because the B-cell lymphoma specific antigens have been adequately described and the nucleic acids have been identified which induce the expression of the antigens.

Therefore, Applicants respectfully request that the written description rejection of claim 34 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

b) Enablement:

Claim 34 was also rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner alleges on page 18 that an undue amount of additional experimentation is required for one of skill in the art to be able to make and use the claimed invention. Applicants respectfully submit that given the level of skill in the art, no undue experimentation is required to practice the invention of claim 34.

For the record, Applicants reiterate that the specification discloses that individual immunostimulatory nucleic acids induce or upregulate the expression of a number of cell surface antigens, including, without limitation, CD19, CD20, CD22, CD40, CD54, CD69, CD80, CD86, MHC Class I, MHC Class II (e.g., HLA-DR), surface immunoglobulin (sIg), and 1D10. Applicants submit that these widely recognized and structurally characterized antigens are representative of antigens that a person of skill in the art would routinely measure to characterize a B cell as malignant or nonmalignant. As to other antigens, Applicants submit that only a

routine amount of experimentation would be required to determine if any given antigen is expressed to a similar or different extent on normal B cells versus malignant or test cells. Furthermore, Applicants submit that, having determined that a given antigen is expressed to a lesser extent on malignant or test cells compared to normal B cells, only a routine amount of experimentation would be required to determine if such antigen is expressed to a greater extent in the presence of immunostimulatory nucleic acid than in its absence.

The foregoing notwithstanding, and solely for the sake of advancing prosecution, claim 34 is currently amended as discussed above to specify both certain antigens and immunostimulatory CpG nucleic acids. It is believed that such amendments overcome the enablement rejection because at most only a routine amount of experimentation may be necessary to practice the invention of claim 34 as currently amended. While some experimentation may be necessary, this does not negate enablement, and Applicants submit that any necessary experimentation would not be undue in view of the detailed description and guidance provided in the specification.

Therefore, Applicants respectfully request that the enablement rejection of claim 34 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Rejections of claim 43 under 35 U.S.C. § 112, first paragraph

a) Written Description:

Claim 43 was rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description. The rejection is based on reasoning essentially parallel to that for the written description rejection of claim 34. Applicants respectfully traverse this rejection.

For the record, and for the sake of brevity, Applicants hereby reiterate with respect to claim 43 the arguments offered above with respect to the written description rejection of claim 34.

The foregoing notwithstanding, and solely for the sake of advancing prosecution, Applicants have amended claim 43 to specify that the surface antigen is selected from CD19, CD20, and CD22. Furthermore, claim 43 is currently amended to specify that the immunostimulatory nucleic acid is an immunostimulatory CpG oligonucleotide between 6 and 100 nucleotides long comprising at least the formula 5′ $X_1X_2CGX_3X_4$ 3′, wherein C is

unmethylated and wherein X_1, X_2, X_3, and X_4 are nucleotides. Applicants submit that claim 43 as currently amended satisfies the written description requirement because the B-cell lymphoma specific antigens have been adequately described and the nucleic acids have been identified which induce the expression of the antigens.

Therefore, Applicants respectfully request that the written description rejection of claim 43 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

b) Enablement:

Claim 43 was also rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The rejection is based on reasoning essentially parallel to that for the enablement rejection of claim 34. Applicants respectfully traverse this rejection.

For the record, Applicants reiterate that the specification discloses that individual immunostimulatory nucleic acids induce or upregulate the expression of a number of cell surface antigens, including, without limitation, CD19, CD20, CD22, CD40, CD54, CD69, CD80, CD86, MHC Class I, MHC Class II (e.g., HLA-DR), surface immunoglobulin (sIg), and 1D10. Applicants submit that these widely recognized and structurally characterized antigens are representative of antigens that a person of skill in the art would routinely test to determine if a particular lymphoma is resistant to therapy with antibodies specific for said antigens. As to other antigens, Applicants submit that only a routine amount of experimentation would be required to determine if any given antigen is expressed to an extent sufficient or not to render the lymphoma sensitive to antibody therapy directed to the antigen. Furthermore, Applicants submit that, having determined that a given lymphoma is resistant to antibody therapy directed to a given antigen, only a routine amount of experimentation would be required to determine if such antigen is expressed to a greater extent in the presence of immunostimulatory nucleic acid than in its absence.

The foregoing notwithstanding, and solely for the sake of advancing prosecution, claim 43 is currently amended as discussed above to specify both certain antigens and immunostimulatory CpG nucleic acids. It is believed that such amendments overcome the enablement rejection because at most only a routine amount of experimentation may be necessary to practice the invention of claim 43 as currently amended. While some

experimentation may be necessary, this does not negate enablement, and Applicants submit that any necessary experimentation would not be undue in view of the detailed description and guidance provided in the specification.

Therefore, Applicants respectfully request that the enablement rejection of claim 43 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Rejections of claim 56 under 35 U.S.C. § 112, first paragraph

a) Written Description:

Claim 56 was rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description. On page 25 of the Office Action, the Examiner alleges that claim 56 encompasses antigens and antibodies which are not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

Applicants wish to point out to the Examiner that claim 56 reflects the unexpected discovery by the inventors that the combination of CpG nucleic acid and an antibody of a particular human isotype, namely IgG1, affords greatly superior cancer cell killing potential compared to CpG in combination with antibodies of another isotype. Thus a key feature of claim 56, in addition to the immunostimulatory CpG nucleic acid, is the antibody isotype, rather than the particular antigen recognized by the antibody. Specifically, for any given cancer cell surface antigen, the claimed invention involves the use of immunostimulatory CpG nucleic acid specifically in combination with an IgG1 antibody, rather than an antibody of another isotype, directed against the cancer cell surface antigen. It is submitted that the invention of claim 56 differs from the inventions of claims 1, 24, 34, and 43 insofar as the former may but need not rely on the induction by the immunostimulatory CpG nucleic acid of a specific cell surface antigen(s) on the cancer cell that is to be killed. Indeed, the claim is directed to any cancer cell surface antigen and an IgG1 antibody directed against said antigen, in combination with an immunostimulatory CpG oligonucleotide between 6 and 100 nucleotides long comprising at least the formula 5′ $X_1X_2CGX_3X_4$ 3′, wherein C is unmethylated and wherein X_1, X_2, X_3, and X_4 are nucleotides. Applicants respectfully submit that no further written description is necessary in

order to convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

So as to remove any possible doubt, Applicants submit that the cell surface antigen of claim 56 can include, but is in no way limited to, CD19, CD20, CD22, CD40, CD54, CD69, CD80, CD86, MHC Class I, MHC Class II (e.g., HLA-DR), surface immunoglobulin (sIg), and 1D10.

Therefore, Applicants respectfully request that the written description rejection of claim 56 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

b) Enablement:

Claim 56 was also rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. On page 25 of the Office Action, the Examiner again refers to the written description guidelines to reject the claim for lack of enablement. The Examiner also alleges on page 26 that there is no indication of any relevant common structural/chemical characteristics, and no identification of any structural limitations/requirements which provide guidance on the identification of surface antigens encompassed by the claim. Applicants respectfully traverse this rejection.

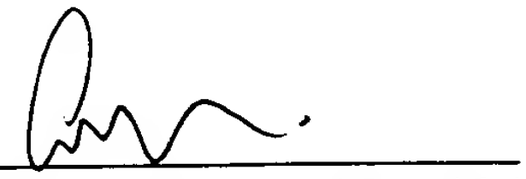
In view of the foregoing discussion with respect to the written description rejection of claim 56, Applicants respectfully submit that claim 56 as currently amended is enabled for the full scope of the claim. In order to practice the method of claim 56, one of skill in the art need only, *inter alia*, ascertain that the cancer cell to be killed expresses a particular cell surface antigen and then select an IgG1 antibody specific for that cell surface antigen. Such steps involve at most only a routine amount of experimentation. Those of skill in the art will recognize that certain expressed cell surface antigens may be preferred over others due to, for example, their level of expression or selective expression on cancer cells as opposed to normal cells. Applicants submit that practice of claim 56 thus entails no more than a reasonable amount of experimentation.

Therefore, Applicants respectfully request that the enablement rejection of claim 56 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

SUMMARY

Applicants believe that claims 1, 5, 7-15, 17-21, 24, 34, 43, and 56 are in condition for allowance. An early and favorable response is earnestly solicited. The Examiner is invited to contact the undersigned by telephone to discuss any remaining issues of patentability.

Respectfully submitted,



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